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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/833,328	04/12/2001	Bernhard Laemmle	R-247.00CIP	3484

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/833,328	LAEMMLE ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *27,28 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26 and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

The Amendment filed on December 3, 2003 is acknowledged. Claims 1-35 are pending in the application. Claim 14, 18, 29 and 31 are amended. Claims 27-28 and 32-35 are withdrawn from consideration as drawn to the non-elected invention. Claims 1-26 and 29-31 are the subject of this Office Action.

DETAILED ACTION

1. Objections

3.1. Specification

Objections to the specification and claim 29 and 31 made in the previous Office Action are withdrawn, because the amendments have been entered.

Claim 29 is, however rejected, because the claim recites the limitation "a composition according to claim 18". There is insufficient antecedent basis for this limitation in the claim, because claim 18 is directed to an isolated polypeptide.

2. Rejections

2.1. 35 USC section 112, second paragraph

Rejection of claim 18 and 29 made in the previous Office Action is withdrawn, because the claims have been amended.

2.2. 35 USC section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 13-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a polypeptide, composition or a complex comprising said polypeptide, having molecular weight between 180 kD and 100 kD and comprising the amino acids sequence of SEQ ID NO: 1. The claims are directed to a large and variable genus of polypeptides whose function and structure is not sufficiently described in the disclosure. The specification teaches several species of the claimed genus, i.e., polypeptides having molecular weight 180 kD and 100 KD and comprising the amino acids sequence of SEQ ID NO: 1 whose function is cleavage of vWF. The specification, however, does not teach the function of other polypeptides having molecular weight between 180 kD and 100 KD and comprising the amino acids sequence of SEQ ID NO: 1. Disclosure of several species of the claimed genus is insufficient to put one skilled in the art in possession of all the species of claimed genus, because the function/structure relationship for the disclosed polypeptides is unknown. Applicants disclose polypeptides having molecular weight 180 kD and 100 KD and comprising the amino acids sequence of SEQ ID NO: 1 whose function is cleavage of vWF but no description has been provided of the common functional features of all polypeptides encompassed by the genus of the claims. No information, beyond the

characterization of SEQ ID NO: 1 and 4 and molecular weight of several bands has been provided by applicants, which would indicate that they had possession of the claimed genus of polypeptides. The claimed genus is diverse in its structure and only several representative species having biological function are disclosed by Applicants. These species are not a representative of all members of the entire genus of polypeptides claimed, and are not sufficient to provide the identifying structural/functional characteristics of the other members of the genus. The disclosure is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

In summary, the claimed polypeptides are insufficiently described in the disclosure, and one skilled in the art cannot reasonably conclude that the Applicants had possession of the claimed invention at the time the instant application was filed.

2.4. 35 USC section 102

Claims 1-26, and 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Furlan et al. (Partial Purification and Characterization of a Protease from Human Plasma Cleaving von Willebrand Factor to Fragments Produced by *in Vivo* Proteolysis, Blood, 1996, 87/10, 4223-4234; copy enclosed). The reasons are stated in the previous office Action and reiterated herein.

The claims are directed to a composition exhibiting von Willebrand factor (vWF) protease activity wherein said composition:

(1) comprises at least one single peptide chain having a molecular weight between 190 and 100 kD, i.e., 180 kD, 170 kD, 160 kD, 120 kD, 110 kD,

wherein said chain comprises the amino acid sequence of SEQ ID NO: 1 or amino acid sequence of SEQ ID NO: 1 followed immediately by the amino acid sequence of SEQ ID NO: 15 or of SEQ ID NO: 4,

(2) cleaves vWF at the peptide bond 842Tyr-843Met,

(4) retains activity in the presence of a serine protease inhibitor (diisopropyl fluorophosphate) and a calpain protease inhibitor (Z-Leu-Leu-Tyr-CHN_2), and

(5) comprises Ca^{2+}, Sr^{2+} or Ba^{2+} ions; and

(6) wherein the amino acid sequence consisting of SEQ ID NO: 1 followed by SEQ ID NO: 15, or amino acid sequence of SEQ ID NO: 4, are encoded by the nucleotide sequence presented in Fig. 2 of the specification.

Furlan et al. disclose a composition obtained (Fig. 6 and 7, page 4228) from human plasma, wherein said composition has the activity of vWF protease (page 4227, left column starting from the subtitle *Purification of the protease*) with cleavage site between 842Tyr-843Met (page 4230 left column starting from the subtitle *Amino acid analysis and amino acid sequence of vWF and its degradation products*), wherein the composition is not inhibited by protease inhibitors (page 4229 left column, starting from the subtitle *Effect of protease inhibitors on vWF degradation*) such as the serine protease inhibitor diisopropyl fluorophosphates (page 4229, right column, line 6) and the calpain protease inhibitor Z-Leu-Leu-Tyr-CHN_2 (page 4229, right column, line 13)

and wherein the composition is the most active in the presence of Ca^{2+}, Sr^{2+} or Ba^{2+} ions (page 4228, right column, starting with the subtitle *Activation by metal ions and pH optimum of the vWF cleavage protease*).

Furlan et al do not particularly teach that the composition contains peptide chains that are between 190 and 100 kD, i.e., 180 kD, 170 kD, 160 kD, 120kD, 110 kD, however one skilled in the art can recognize in Fig. 7 of the article the bands corresponding to the enumerated molecular weights. These bands are presented together with their molecular weights in Table 1 of the specification.

Furlan et al. do not teach the polypeptide whose N-terminal comprises SEQ ID NO: 1 or SEQ ID NO: 4 or SEQ ID NO: 1 immediately followed by SEQ ID NO: 15, or the polypeptide whose N terminus is SEQ ID NO: 4. However, SEQ ID NO: 1, and 4 and 15 are inherent features of the C-terminal truncated forms of the very vWF protease that is disclosed by Furlan at al. and are inheritently encoded by the DNA of Fig. 2.

Although Furlan et al. do not particularly teach that the composition contains peptide chains that comprise amino acid of SEQ ID NO: 1 or amino acid sequence of SEQ ID NO: 1 followed immediately by the amino acid sequence of SEQ ID NO: 15 or amino acid of SEQ ID NO: 4, Table 2 of the specification, as well as Table 2 of the paper by Gerritsen et al. (Partial amino acid sequence of purified von Willebrand factor-cleaving protease, Blood, 2001, 96, 1654-1661) clearly show that each of the bands of molecular weights 150 kD, 140 kD, 130 kD, 110 kD unreduced, and 180 kD, 170 kD, 169 kD and 120 kD reduced do have the recited N-terminal that starts with SEQ ID NO:1 or SEQ ID NO: 1 immediately followed by SEQ ID NO:15, when long enough

streches of the N- terminal part of the protein were sequenced. The paper by Gerritsen et al. shows that characteristics not disclosed in the reference by Furlan et al. is inherent; see MPEP 2131.01 "Multiple Reference in 35 U. S.C. 102 Rejections [R-1] (C).

Since the Office does not have the facilities for examining and comparing Applicants' protein with the protein of the prior art, the burden is on Applicants to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Traversing this rejection Applicants write in their Response, "Furlan et al. refer to the proteins having a M_w other than 300 kD on an unreduced SDS-PAGE gel, inculding, *inter alia*, protein bands in the range between 180 and 130 kD, as '*contaminating proteins*' (see, e.g., page 4228, first column, line 7, bridging to second column, line 5) (emphasis added), and thus not vWF protease" (page 9 line 10). On page 10, line 8, Applicants continue, "Furlan et al. reference is not properly enabled. For a reference to be anticipatory under 35 U.S.C. § 102(b), the reference must be enabling, i.e., the reference must contain a description of the claimed invention in such full, clear, and exact terms as to enable any person

skilled in the art to which it pertains to make and use the same."

Applicants' arguments have been fully considered, but are found not persuasive for the following reasons.

Indeed, Furlan and co-workers' strong opinion is that bands of 180 kD, 170 kD, 160kD, 120 kD, 110 kD visible in the unreduced SDS-PAGE gel are "contaminating proteins", i.e., proteins that has nothing to do with the proteolytic activity directed to vWF. However, the publication teaches in detail how to obtain these bands, and one skilled in the art could obtain them without difficulty. Therefore, these bands are enabled, although not described as the truncated forms of the enzyme. Thus, because the reference is enabling, it is anticipatory.

The question of enablement in a reference is addressed in MPEP 2121-2122. Section 2122 states that UTILITY NEED NOT BE DISCLOSED IN REFERENCE; in the instant case utility is the function of protease cleaving vWF which is not attributed by Furlan and co-workers to the bands of 180 kD, 170 kD, 160kD, 120 kD, 110 kD. However, section 2122 reads:

> "In order to constitute anticipatory prior art, a reference must identically disclose the claimed compound, but no utility need be disclosed by the reference. In re Schoenwald, 964 F.2d 1122, 22 USPQ2d 1671 (Fed. Cir. 1992) (The application claimed compounds used in ophthalmic compositions to treat dry eye syndrome. The examiner found a printed publication which disclosed the claimed compound but did not disclose a use for the compound. The court found that the claim was anticipated since the compound and a process of making it was taught by the reference. The court explained that 'no utility need be disclosed for a reference to be anticipatory of a claim to an old compound.' 964 F.2d at 1124, 22 USPQ2d at 1673. It is enough that the claimed compound is taught by the reference.)."

Applicants also argue, page 9, line 26, "The second reference relied on by the Examiner, Gerritsen et al., has a publication [date] after Applicants' priority date."

This argument of Applicants is found not persuasive because the use of additional reference to show that the cited reference meets all limitations of the claim is appropriate. Gerritsen et al. Reference is used only to show that claimed features are inherently present in the compounds disclosed by Furlan et al. MPEP 2131.01, part III. TO SHOW THAT A CHACTERISTIC NOT DISCLOSED IN THE REFERENCE IS INHERENT, states: "Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation." See the enclosed copy.

3. Conclusion

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944 and the right fax number is (571) 273-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. EST.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

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Continuation of Attachment(s) 6). Other: copy of the MPEP page.